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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Contact Lens Care Product for Hard and Soft Contact Lenses

(72) Schwind, Peter - Germany (Federal Republic of) ;

(71) Ciba-Geigy AG - Switzerland ;

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(57) 15 Claims

CL/V-19128/A/CVE 34

Contact lens care product for hard and soft contact lenses

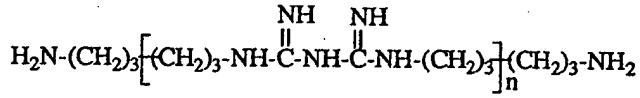
The present invention relates to a contact lens care product for hard and soft contact lenses, comprising a (poly)aminopropyl biguanide and a special buffer.

Contact lens care products comprising an aminopropyl biguanide are already known. For example, GB 1 432 345 describes ophthalmic compositions and compositions for disinfecting contact lenses comprising an ophthalmologically acceptable polymeric biguanide. Only phosphate buffers are disclosed as suitable buffers in that context.

EP-A1-180 309 also discloses disinfecting and preserving solutions for contact lenses, comprising a biguanide and a buffer. The biguanide is again of the aminopropyl biguanide type. As buffer especially borate buffers are proposed. Additional buffers mentioned are citrate buffers, bicarbonate buffers and mixed phosphate buffers.

In contrast, the present invention relates to contact lens care products comprising an aminopropyl biguanide or a salt thereof and as buffer the so-called tris buffer (trometamol) or a homolog thereof having up to 10 carbon atoms or a salt thereof. The invention relates also to the use of such a contact lens care product for cleaning and disinfecting contact lenses.

The aminopropyl biguanides to be used according to the invention are especially those of formula I



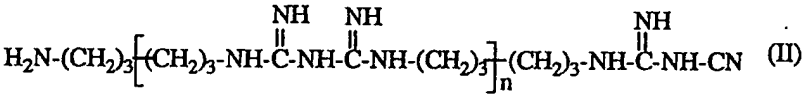
(I)

wherein n is an integer from 1 to 500; it is also possible to use salts of compounds of formula I, especially ophthalmologically acceptable salts thereof.

The compounds of formula I are known. Their preparation is described, for example, in

GB 702 268 and GB 1 152 243. In addition, those compounds are also commercially available, for example as Vantocil®, Cosmocil® or as Arlagard®E from ICI Chemicals.

Depending on the manner in which they have been prepared, the compounds of formula I may comprise certain amounts of a secondary product of formula II



(II)

or salts thereof, wherein n is likewise an integer from 1 to 500. Mixtures of compounds of formula I with those of formula II can likewise be used according to the invention. The proportion of compounds of formula II, based on the total amount of compounds of formula I and compounds of formula II, is preferably less than 20 percent by weight, more preferably less than from 2 to 10 percent by weight and is especially preferably zero percent by weight.

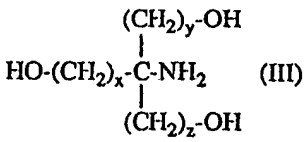
The index n in formulae I and II is preferably from 1 to 200, especially from 2 to 100, more especially from 2 to 50 and most especially from 3 to 12. Depending on the value of the index n in formula I or II, the molecular weight of the aminopropyl biguanides that can be used is as low as the molecular weight of the monomer of formula I (n = 1), or in the range of approximately 600 to 1600 if oligomers are used, i.e. when n is, for example, from 3 to 8, or alternatively in the range of from approximately 50 000 to approximately 90 000 if n is significantly higher, for example approximately 270 to 500.

In the contact lens care products according to the invention, the compound of formula I is used preferably in an amount, based on the total amount of the contact lens care product, which is advantageously formulated as an aqueous solution, of from 0.1 to 100 ppm (0.00001 - 0.01 percent by weight), especially in an amount of from 0.5 to 50 ppm (0.00005 - 0.005 percent by weight) and more especially in an amount of from 1 to 10 ppm (0.0001 - 0.001 percent by weight), for example 1, 2 or 5 ppm.

Salts of compounds of formula I and formula II that are suitable within the scope of the present invention are water-soluble salts that are advantageously ophthalmologically acceptable. Suitable salts are those with inorganic or organic acids, for example hydrochlorides, hydrobromides, borates, acetates, gluconates, sulfonates, maleates, ascorbates,

tartrates or citrates.

The trometamol and its homologs having up to 10, preferably from 5 to 7, carbon atoms used according to the invention preferably are the compounds of formula III



(III)

wherein x, y and z are each independently of the others an integer, at least 1, and the sum of x, y and z is from 3 to 9, preferably from 3 to 6, or a salt thereof. Special preference is given to 2-amino-2-hydroxymethyl-1,3-propanediol (trometamol), which corresponds to a compound of formula III wherein each of x and y and z is 1. The compound trometamol is also referred to as tris buffer.

Trometamol and its homologs having up to 10 carbon atoms are already known. Their use in medicaments for the treatment of inflammations of the eye has already been disclosed in EP-A2-242 328. Compositions for the disinfection of contact lenses, comprising 1.2 % tromethamine/tromethamine hydrochloride and 1 ppm polyhexamethylene biguanide hydrochloride, are already known from WO 92/11876. Compounds of formula III are, moreover, also commercially available.

The amount of trometamol used as buffer in the contact lens care products according to the invention, based on the total amount of the contact lens care product, is preferably from 0.05 to 5 percent by weight, preferably from 0.1 to 2.5 percent by weight and especially preferably from approximately 0.2 to approximately 1.5 percent by weight. The amount of trometamol used as buffer in the contact lens care products according to the invention, based on the total amount of the contact lens care product, is more especially from 0.05 to less than 1.2 percent by weight or from 0.05 to less than 0.8 percent by weight, very especially from 0.1 to 0.6 percent by weight, especially from 0.1 to less than 0.6 percent by weight, for example up to 0.5 percent by weight.

2-Amino-2-hydroxymethyl-1,3-propanediol or a homolog thereof having up to 10 carbon atoms, or a salt thereof, can be used alone as buffer. Alternatively, one of the above-mentioned compounds can be used together with a salt thereof. Again, preference is given

here to the use of ophthalmologically acceptable salts, such as the salts mentioned above in connection with compounds of formula I. Especially suitable are the hydrochlorides or maleates of compounds of formula III, i.e., for example, a combination of 2-amino-2-hydroxymethyl-1,3-propanediol with the hydrochloride of 2-amino-2-hydroxymethyl-1,3-propanediol, or a combination of 2-amino-2-hydroxymethyl-1,3-propanediol with the maleate of 2-amino-2-hydroxymethyl-1,3-propanediol or 2-amino-2-hydroxymethyl-1,3-propanediol, to which small amounts of hydrochloric acid are added.

The contact lens care products according to the invention preferably do not comprise buffers other than compounds of formula III. They may, however, comprise other buffers in addition to one or more compounds of formula III.

The contact lens care products according to the invention are preferably formulated in such a manner that they are isotonic with lachrymal fluid. They may in general comprise additives that are customary for contact lens care products. Those include, for example, compounds that influence tonicity, surface-active compounds, compounds that influence viscosity, or complex formers. The contact lens care products according to the invention comprise those or other customary additives in amounts that vary within the range of the values familiar to the person skilled in the art.

A solution that is isotonic with lachrymal fluid is generally understood to be a solution the concentration of which corresponds to the concentration of a 0.9 % sodium chloride solution. Departures therefrom are entirely possible, provided that the contact lenses to be treated are not damaged thereby. Isotonicity with lachrymal fluid or a different desired tonicity can be established by the addition of organic or inorganic compounds that influence tonicity. The former can be used, for example, in amounts of approximately 1 to 4.5 percent by weight, the latter in amounts of approximately 0.1 to 1.3 percent by weight. In general, the amount of the compound that influences tonicity that is added is such that the tonicity of the composition according to the invention is especially in the range of from 200 to 450 milliosmols, preferably in the range of from approximately 270 to approximately 330 milliosmols. Typical organic compounds of that type are, for example, glycerol, urea, propylene glycol or sugars, such as mannitol or sorbitol, and typical inorganic compounds of that type are especially potassium chloride and sodium chloride. Mixtures of those compounds with one another can also be used according to the invention.

Suitable surface-active compounds are mentioned, for example, in EP-A2-180 309. Examples of especially suitable representatives that can be used according to the invention are poloxamer types and miranol types. Other representatives are known to a person skilled in the art. Those compounds can be used, for example, in amounts of up to 20 percent by weight, especially in amounts of from 0.4 to 5 percent by weight.

Suitable compounds that influence viscosity are also known to a person skilled in the art. Examples of especially suitable representatives that can be used according to the invention are polyvinyl alcohol, hydroxyethylcellulose, hydroxypropylmethylcellulose and polyacrylic acid. Typical amounts for those compounds are from 0.1 to 2 percent by weight.

An especially suitable complex former is especially ethylenediaminetetraacetic acid, abbreviated to EDTA, and salts thereof, such as sodium salts. Typical amounts for those compounds are from 0.01 to 1 percent by weight.

The contact lens care products according to the invention are suitable for all types of contact lenses. These include especially so-called hard and soft contact lenses, and also so-called hard-flexible or highly gas-permeable contact lenses. The contact lens care products according to the invention exhibit an antimicrobial action and, also, a cleaning action. Depending on the specific intended use, the contact lens care products according to the invention can be used as cleaning solutions, disinfectants, or, for example, as solutions for storing, rinsing, wetting or soaking contact lenses. All those solutions are distinguished by good cleaning and disinfecting action and a high degree of tolerability in a single solution.

In addition, while exhibiting better antimicrobial activity, the contact lens care products according to the invention surprisingly exhibit significantly better cytotoxicity properties than do the care products known from the prior art, for example Bausch & Lomb's Kombi solution. The overall spectrum of properties of the contact lens care products according to the invention is therefore considered to be significantly superior to the properties of the contact lens care products known from the prior art.

The contact lens care products according to the invention are prepared in a manner known per se, especially by conventional mixing of the constituents with water or dissolving of the constituents in water.

The compositions according to the invention are especially suitable for cleaning and disinfecting contact lenses. The contact lens care products according to the invention are used in a manner known per se, for example by bringing a contact lens into contact with the contact lens care product for a period of time sufficient for cleaning or disinfection. Depending on the type of lens and the degree of contamination, a period of from several minutes to about 24 hours, preferably up to approximately 4 to 12 hours, is sufficient.

A preferred solution according to the invention comprises, for example,

aminopropyl biguanide	0.0005 to 0.05 mg/ml
2-amino-2-hydroxymethyl-1,3-propanediol	0.67 to 4.03 mg/ml
2-amino-2-hydroxymethyl-1,3-propanediol . HCl	2.64 to 4.02 mg/ml,

the total amount of buffer being preferably less than 8 mg/ml and especially less than 6 mg/ml,

and may preferably also comprise:

NaCl or KCl	3 to 9 mg/ml especially 5.5 to 9 mg/ml
surface-active compound	5 to 30 mg/ml
EDTA	0.1 to 2 mg/ml.

A solution according to the invention that is likewise preferred comprises, for example,

aminopropyl biguanide	0.0005 to 0.05 mg/ml
2-amino-2-hydroxymethyl-1,3-propanediol	1.00 to 4.00 mg/ml especially about 2.5 mg/ml

and small amounts of HCl to establish the desired pH range.

The desired pH range of the compositions according to the invention is especially approximately 7.0 to 7.5, preferably from 7.1 to 7.4 and especially preferably 7.3.

The following Examples serve to illustrate the invention. They are not, however, intended to limit the scope of the invention in any way, and especially not to the subject-matter of the Examples.

Example 1: Formulation for soft contact lenses
1 ml of solution comprises:

aminopropyl biguanide (Arlagard®)	0.005 mg
2-amino-2-hydroxymethyl-1,3-propanediol	0.97 mg
2-amino-2-hydroxymethyl-1,3-propanediol · HCl	6.61 mg
NaCl	6.6 mg
poloxamer 407	10 mg
EDTA	1 mg.

Example 2: Formulation for hard contact lenses
1 ml of solution comprises:

aminopropyl biguanide (Arlagard®)	0.005 mg
2-amino-2-hydroxymethyl-1,3-propanediol	0.97 mg
2-amino-2-hydroxymethyl-1,3-propanediol · HCl	6.61 mg
NaCl	6.6 mg
poloxamer 407	10 mg
EDTA	1 mg
polyvinyl alcohol	14 mg.

Example 3: Formulation for soft contact lenses
1 ml of solution comprises:

aminopropyl biguanide (Arlagard E®)	0.005 mg
2-amino-2-hydroxymethyl-1,3-propanediol	1.39 mg
2-amino-2-hydroxymethyl-1,3-propanediol · HCl	6.06 mg
NaCl	5.5 mg
poloxamer 407	10 mg
EDTA	1 mg.

Example 4: Antimicrobial activity
The formulation of Example 3 is tested against the following test organisms: Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans, Aspergillus niger. The following Table shows the initial inoculum as well as the number of organisms

still to be found after the formulation of Example 3 has been allowed to act for a period of 4 hours and of 6 hours:

Test organism	initial inoculum	number of organisms after 4 hours	number of organisms after 6 hours
Escherichia coli	$6.8 \cdot 10^5$	0	0
Staphylococcus aureus	$8.9 \cdot 10^5$	0	0
Pseudomonas aeruginosa	$1.0 \cdot 10^6$	0	0
Candida albicans	$1.1 \cdot 10^6$	$2.7 \cdot 10^5$	$1.8 \cdot 10^5$
Aspergillus niger	$1.1 \cdot 10^6$	$6.2 \cdot 10^5$	$1.1 \cdot 10^6$

In contrast, the following values are determined for Bausch & Lomb's Renu solution comprising aminopropyl biguanide (0.5 ppm) and a borate buffer:

Test organism	initial inoculum	number of organisms after 4 hours	number of organisms after 6 hours
Escherichia coli	$6.8 \cdot 10^5$	$9.5 \cdot 10^1$	$4.3 \cdot 10^1$
Staphylococcus aureus	$8.9 \cdot 10^5$	$5.7 \cdot 10^1$	$3.8 \cdot 10^1$
Pseudomonas aeruginosa	$1.0 \cdot 10^6$	0	0
Candida albicans	$1.1 \cdot 10^6$	$4.9 \cdot 10^5$	$6.2 \cdot 10^5$
Aspergillus niger	$1.1 \cdot 10^6$	$5.5 \cdot 10^5$	$4.3 \cdot 10^5$

Example 5: Cytotoxicity test

In order to determine the cytotoxic potential, the formulation of Example 3 is subjected to the growth inhibition test and compared with Bausch & Lomb's Kombi solution. In this test the decrease in cell growth in the presence of toxic compounds is determined by comparing the protein content of treated cell cultures with the protein content of untreated cell cultures after 72 hours' incubation. The test solutions are serially diluted with the cell culture medium (DMEM-FCS). L 929 cell cultures are incubated for 72 hours in the presence of solutions of various concentrations. It is found that the solution according to

presence of solutions of various concentrations. It is found that the solution according to the invention induces cytotoxic effects only at concentrations of 20 % v/v, while the Kombi solution already induces cytotoxic effects at concentrations of 5 % v/v.

In the test carried out, the protein content is a measure of the cell growth or the inhibition of growth induced by toxic substances. Growth inhibition of more than 30 % compared with untreated cultures is considered to be a clear cytotoxic effect.

Solution A): Formulation according to Example 3

Concentration of the solution [% v/v]	20.0	10.0	5.0	2.5	1.3	0.6
Growth inhibition [%]	32	11	4	4	2	0

Solution B): Kombi solution from Bausch & Lomb

Concentration of the solution [% v/v]	20.0	10.0	5.0	2.5	1.3	0.6
Growth inhibition [%]	92	68	40	25	11	7

These results demonstrate that the Kombi solution already induces cytotoxic effects at a dilution lower by a factor of 4, namely at 5 % v/v, compared with the formulation according to Example 3 with which such effects occur only with 20 % v/v solutions.

Example 6: Formulation for hard contact lenses

1 ml of solution comprises:

polyaminopropyl biguanide (Cosmocil®)	0.002 mg
2-amino-2-hydroxymethyl-1,3-propanediol	2.5 mg
NaCl	7.5 mg
poloxamer 407	10 mg
hydroxyethylcellulose	3.2 mg
EDTA	1 mg
HCl to adjust pH	

Example 7: Formulation for soft contact lenses

1 ml of solution comprises:

polyaminopropyl biguanide (Cosmocil®)	0.001 mg
2-amino-2-hydroxymethyl-1,3-propanediol	2.45 mg
NaCl	7.4 mg
poloxamer 407	1.0 mg
EDTA	0.25 mg
HCl to adjust pH	

Example 8: Antimicrobial activity

The formulation according to Example 6 is tested against the following test organisms: Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans, Aspergillus niger. The following Table indicates the initial inoculum and the number of organisms still to be found after the formulation of Example 6 has been allowed to act for a period of 6 hours:

Test organism	initial inoculum	number of organisms after 6 hours
Escherichia coli	$1.1 \cdot 10^6$	0
Staphylococcus aureus	$1.4 \cdot 10^6$	0
Pseudomonas aeruginosa	$1.3 \cdot 10^6$	0
Candida albicans	$1.2 \cdot 10^6$	$4.1 \cdot 10^5$
Aspergillus niger	$5.7 \cdot 10^5$	$2.8 \cdot 10^5$

Example 9: Cytotoxicity test

Analogously to Example 5 the formulation according to Example 6 is subjected to the growth inhibition test. The test shows that the solution according to the invention induces only extremely slight cytotoxic effects even at concentrations of 20 % v/v, while the Kombi solution already induces significant cytotoxic effects at concentrations of 5 % v/v (see Example 5).

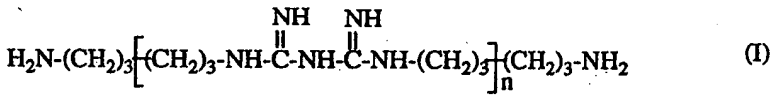
Solution according to Example 6

Concentration of solution [% v/v]	20.0	10.0	5.0	2.5	1.3	0.6
growth inhibition [%]	12	5	0	0	0	3

What is claimed is:

1. A contact lens care product comprising an aminopropyl biguanide or a salt thereof and as buffer trometamol or a homolog thereof having up to 10 carbon atoms or a salt thereof.

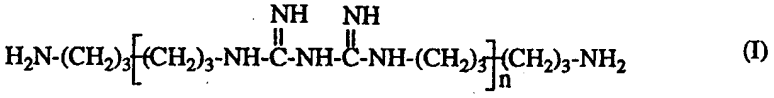
2. A contact lens care product according to claim 1 wherein the aminopropyl biguanide is a compound of formula I



(I)

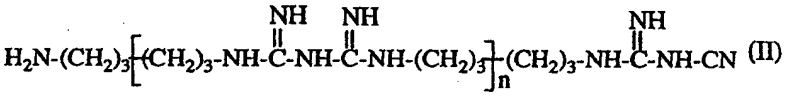
wherein n is an integer from 1 to 500, or a salt of a compound of formula I.

3. A contact lens care product according to claim 1 wherein the aminopropyl biguanide is a mixture of a compound of formula I, or a salt thereof,



(I)

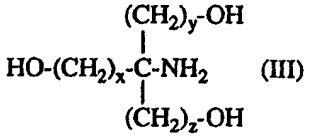
wherein n is an integer from 1 to 500, with a compound of formula II, or a salt thereof,



(II)

wherein n is likewise an integer from 1 to 500.

4. A contact lens care product according to claim 1 wherein the buffer is a compound of formula III

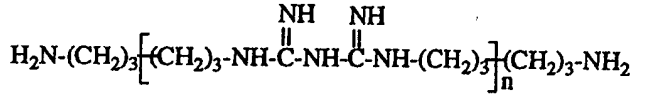


(III)

wherein x, y and z are each independently of the others an integer, at least 1, and the sum

of x, y and z is from 3 to 9, or a salt thereof.

5. A contact lens care product according to claim 1 wherein the aminopropyl biguanide is a compound of formula I



(I)

wherein n is an integer from 1 to 500, or a salt of a compound of formula I, and wherein the buffer is trometamol or a salt thereof.

6. A contact lens care product according to claim 1 comprising from 0.05 to less than 1.2 percent by weight trometamol or a homolog thereof having up to 10 carbon atoms or a salt thereof.

7. A contact lens care product according to claim 1 comprising from 0.05 to less than 0.8 percent by weight trometamol or a homolog thereof having up to 10 carbon atoms or a salt thereof.

8. A contact lens care product according to claim 1 comprising from 0.1 to 0.6 percent by weight trometamol or a homolog thereof having up to 10 carbon atoms or a salt thereof.

9. A contact lens care product according to claim 5 comprising from 0.1 to 0.6 percent by weight trometamol or a homolog thereof having up to 10 carbon atoms or a salt thereof.

10. A contact lens care product according to claim 1 comprising

aminopropyl biguanide	0.0005 to 0.05 mg/ml
2-amino-2-hydroxymethyl-1,3-propanediol	1.00 to 4.00 mg/ml especially about 2.5 mg/ml

and HCl to establish a pH of from 7.0 to 7.5.

11. A contact lens care product according to claim 1 comprising in addition one or more additives selected from compounds that influence tonicity, surface-active compounds, compounds that influence viscosity and complex formers.

12. A contact lens care product according to claim 1 comprising

polyaminopropyl biguanide (Cosmocil®)	0.002 mg/ml
2-amino-2-hydroxymethyl-1,3-propanediol	2.5 mg/ml
NaCl	7.5 mg/ml
poloxamer 407	10 mg/ml
hydroxyethylcellulose	3.2 mg/ml
EDTA	1 mg/ml

and HCl to adjust the pH.

13. A contact lens care product according to claim 1 comprising

aminopropyl biguanide (Cosmocil®)	0.001 mg/ml
2-amino-2-hydroxymethyl-1,3-propanediol	2 mg/ml
NaCl	7.4 mg/ml
poloxamer 407	1.0 mg/ml
EDTA	0.25 mg/ml

and HCl to adjust the pH.

14. The use of a contact lens care product according to claim 1 for cleaning and/or disinfecting a contact lens.

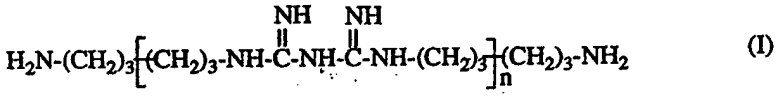
15. A method of cleaning and/or disinfecting a contact lens which comprises bringing a contact lens care product according to claim 1 into contact with a contact lens for a period of time sufficient for cleaning or disinfection.

CL/V-19128/A/CVE 34

Contact lens care product for hard and soft contact lenses

Abstract

The present invention relates to contact lens care products comprising an aminopropyl biguanide or a salt thereof, especially a compound of formula I



(I)

wherein n is an integer from 1 to 500, or a salt thereof, and the so-called tris buffer (trometamol) or a homolog thereof having up to 10 carbon atoms or a salt thereof. The invention relates also to the use of such a contact lens care product for cleaning and disinfecting contact lenses.